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Early and late abdominal surgeries after lung transplantation: incidence and outcome[†]

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CONCLUSIONS: Early abdominal surgeries after lung transplantation are associated with a significant mortality risk. Abdominal operations at late time points have a favourable outcome unless patients were hospitalized prior to the abdominal complication.

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Keywords: Lung transplantation • Complications • Abdominal complications • Survival

INTRODUCTION

Lung transplantation is the therapy of choice for chronic end-stage lung diseases [1]. Over time, long-term survival improved with multidisciplinary treatment, including better surgical technique, intensive care management and immunosuppression. However, lung transplant candidates are often seriously ill, vulnerable and subsequently exposed to the transplant procedure and immunosuppression. Abdominal surgery in the postoperative course of lung transplantation is a known factor for major morbidity and mortality [2–5]. In this report, we describe our clinical experience and outcome of early abdominal surgery and late abdominal surgery after lung transplantation. We defined early abdominal surgery as that which occurs during the initial hospitalization after lung transplantation, different to the definition of ‘occurring during

the first 30 days after lung transplantation’. This has higher impact on the treatment of patients during the initial vulnerable time. The objective of this study was to mainly describe the frequency of abdominal surgical interventions, outline their outcome and to assess the potential risk factors.

METHODS

This retrospective study includes 315 patients who underwent lung transplantation between January 2000 and December 2013 at the Zurich University Hospital. There were no exclusion criteria. As part of informed consent, all patients signed an agreement at the time of the treatment, which allows the involved physicians of the university hospital to use their data for scientific research. The ethics committee approved the study (ZH-KEK-Nr. 2014-0244).

Patients who underwent abdominal surgery after lung transplantation were included in this study. It has to be mentioned

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that patients with serious pre-existing abdominal illness were not candidates for lung transplantation and, therefore, not included in this cohort. Diseases concerning the urinary tract were not included. 'Early surgery' was defined as procedures performed during hospitalization for lung transplantation. Any abdominal surgery after the discharge for lung transplantation was considered as 'late surgery'. In case of repeated surgery (e.g. for open abdomen), only the first procedure was reported. Complications were classified with the Clavien–Dindo classification [6].

To prevent abdominal complications after lung transplantation, different strategies were followed since then. One issue that needs special attention is intestinal motility, which is frequently reduced by many factors (drugs, immobilization, etc.). As obstipation or coprostasis generally remains asymptomatic or oligo-symptomatic initially, and complications are potentially severe, we emphasize the need for daily bowel movements from postoperative day 2 onwards and, therefore, provided adequate administration of laxatives. Osmotic active laxatives (such as macrogolum 3350) and radiocontrast agents (natrii amidotrizoas/meglumini amidotrizoas orally 20–40 ml 3 times daily) and, especially in cystic fibrosis patients, oral high-dose N-acetyl-cysteine (up to 5 g per dose, mixed with orange juice to attenuate the bad smell or taste). With this strategy, we aim to prevent some of the early severe gastrointestinal complications [7]. Regular abdominal examinations were performed, and in case of suspicion, an abdominal X-ray or computed tomography (CT) scan was taken.

Statistical analyses

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS version 22.0). Non-normal variables are presented as median \pm interquartile range (IQR) and compared using the Mann–Whitney *U*-test. Statistical correlation between 2 parameters was analysed using the Pearson's χ^2 test. Survival rate was calculated using the Kaplan–Meier method. The censor date for all survival data was 30 June 2014. Follow-up was defined as the time between the date of lung transplantation and the date of death or the date of the latest follow-up (censor date). The time between the date of lung transplantation and the date of abdominal surgery is defined as 'time between lung transplantation and abdominal surgery'. The log-rank test was used to compare the survival curve from patients with and without abdominal surgery. The Cox regression analysis was used to determine risk factors for the occurrence of abdominal surgery.

The most important limitations of this study are the retrospective study design and the small sample size. One option to enlarge the sample size would be involving patients from a longer time interval, which has the disadvantage that medical management of complications may have changed over a longer period of time (different eras). Multicentre studies, as another option, may be difficult to perform because of different management standards relating to prevention and treatment of transplantation-related complications.

RESULTS

Demographic data

In total, 315 patients underwent lung transplantation between 2000 and 2013 at the Zurich University Hospital. The analysed cohort included 169 (54%) men and 146 (46%) women, with a

Table 1: Demographic data of the study population

Cases of LuTx between 2000 and 2013	<i>n</i> = 315
Male/female gender, <i>n</i> (%)	169 (54)/146 (46)
Age (years), median (IQR)	50 (30–59)
Diagnosis, <i>n</i> (%)	
CF	103 (33)
COPD	72 (23)
IPF	71 (23)
A1ATD	16 (5)
PPH	12 (4)
Others	41 (13.0)
Bilateral transplantation, <i>n</i> (%)	302 (96)
Intraoperative ECMO use, <i>n</i> (%)	157 (50)

A1ATD: alpha-1 antitrypsin deficiency; ECMO: extracorporeal membrane oxygenation; CF: cystic fibrosis; COPD: chronic obstructive lung disease; IPF: idiopathic pulmonary fibrosis; IQR: interquartile range; LuTx: lung transplantation; PPH: primary pulmonary hypertension.

median age of 50 years (IQR 30–59 years) at the time of transplantation. Underlying diseases are reported in Table 1. Bilateral lung transplantation was performed in 96% of patients. Ten patients underwent retransplantation during the study period.

Abdominal surgery after lung transplantation

Fifty-two patients developed abdominal diseases requiring surgery: *n* = 16 (5%) in the early postoperative phase and *n* = 42 (13%) after discharge. Therefore, 6 patients were in need of abdominal surgery in the early postoperative phase and the late postoperative phase. The late abdominal surgery in 3 of these patients was related to the early abdominal surgery, mainly because of surgical revision of incisional hernia. In the 3 other patients, choledocholithiasis, small bowel bleeding and perforated diverticulitis occurred during later time course.

Among the 52 patients who underwent abdominal surgery at any time, 40% were women and 60% were men with a median age of 51 years (IQR 36–59 years) at the time of lung transplantation. The main diseases leading to transplantation were cystic fibrosis in 31% of patients, chronic obstructive lung disease (COPD) in 31% of patients, idiopathic pulmonary fibrosis in 17% of patients and A1ATD in 12% of patients. Except 1 patient, all underwent bilateral transplantation, and intraoperative extracorporeal membrane oxygenation (ECMO) was used in 40% of patients.

In patients with an early abdominal surgery, 25% were women and 75% were men. The median age of these patients at the time of lung transplantation was 59 years (IQR 54–63 years), and 31% of patients experienced COPD or idiopathic pulmonary fibrosis and 25% of patients experienced A1ATD. All patients except 1 patient underwent bilateral transplantation, and ECMO was used in 25% of patients during transplantation.

Among the 36 patients who underwent only late abdominal surgery, 47% were women and 53% were men with a median age of 43 years (IQR 32–55 years) at the time of transplantation. The most common diseases in these patients were cystic fibrosis in 44% of patients and COPD in 31% of patients. All these patients underwent bilateral transplantation, and intraoperative ECMO was necessary in 47% of patients.

Table 2: Characteristics of early and late abdominal diseases requiring surgery

	Early surgery	Late surgery
Number of affected patients, <i>n</i> (%)	16 (5)	42 (13)
Number of events, <i>n</i>	16	52
Time after LuTx (days), median (IQR)	7 (4–13)	1136 (469–2404)
Initial hospitalization cause, <i>n</i> (%)		
Abdominal complication	0	42 (81)
Lung transplantation /pulmonary disease	16 (100)	6 (12)
Kidney disease	0	1 (2)
Others ^a	0	3 (6)
Type of abdominal disease, <i>n</i> (%)		
Ischaemia	7 (44)	0
Perforation/inflammation	4 (25)	19 (37)
Ileus	1 (6)	9 (17)
Malignancy	0	8 (15)
Others ^b	4 (25)	16 (31)
Site of disease, <i>n</i> (%)		
Small bowel	2 (13)	12 (23)
Cecum/ascending colon	8 (50)	0
Transverse colon	0	3 (6)
Descending colon/sigma	0	10 (19)
Appendix	0	2 (4)
Biliary system	0	9 (17)
Others ^c	6 (38)	15 (29)
Unknown	0	1 (2)
Open/laparoscopic intervention, <i>n</i> (%)	16 (100)/0	39 (75)/13 (25)
Bowel resection without anastomosis	6 (38)	10 (19)
Bowel resection with anastomosis	5 (31)	7 (14)
Others	5 (31)	35 (67)
Stoma/stoma reversal, <i>n</i>	12/4	15/4
Emergency/elective, <i>n</i> (%)	16 (100%)/0	29 (56%)/23 (44%)
Reoperation: yes/no, <i>n</i> (%)	9 (56%)/7 (44%)	13 (25.0%)/39 (75%)
Conservative treatment before surgery: yes/no, <i>n</i> (%)	6 (38%)/10 (63%)	15 (29%)/37 (71%)
Hospitalization time in days after first intervention, median (IQR)	43 (26–63)	23 (9–48)

^aLymphocele inguinal, metabolic–toxic encephalopathy and acute ischaemia in the leg.

^bSmall bowel bleeding, abscess after PEG, abdominal bleeding (not verified), chylaskos, diarrhoea, Olgivie syndrome, stomach fistula, rectum prolapse and gall-bladder hydrops.

^cAbdominal wall, rectum, stomach and liver.

IQR: interquartile range; LuTx: lung transplantation.

Table 3: Univariable analysis of risk factors

Variables	Early			Late		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (years)	1.05	0.98–1.12	0.18	1.02	0.98–1.07	0.28
Female gender	1.14	0.23–5.66	0.87	1.75	0.49–6.19	0.39
Diagnosis			0.29			0.09
COPD	1.17	0.11–12.9	0.9	4.12	1.08–15.56	0.04
IPF	3.79	0.63–22.66	0.15	1.12	0.12–10.33	0.92
ECMO use	1.06	0.22–5.27	0.94	0.62	0.16–2.39	0.48
Operation time	0.99	0.98–1.00	0.26			

CI: confidence interval; COPD: chronic obstructive lung disease; ECMO: extracorporeal membrane oxygenation; HR: hazard ratio; IPF: idiopathic pulmonary fibrosis.

An overview of abdominal complications and interventions is given in Table 2. The investigated risk factors for the development of early and late abdominal problems requiring surgery are listed in Table 3. No statistically significant risk factor could be identified, except the diagnosis of COPD for late abdominal surgery.

Early abdominal surgery after lung transplantation

The most common abdominal complication requiring surgery in the early phase after lung transplantation was bowel ischaemia (*n* = 7, 44% of all early events) and bowel perforation (*n* = 4, 25% of all early events), resulting in total of 42 interventions.

Ischaemia was due to volvulus ($n=2$) and mesenteric ischaemia ($n=5$). The most often affected site was the right colon ($n=8$, 50% of all early events). Those early events occurred 7 days (IQR 4–13 days) after lung transplantation. The median hospitalization time after lung transplantation of patients with early abdominal surgery was significantly longer [58 days, compared to 36 days in patients without abdominal surgery ($P=0.02$)]. Mortality was 38% ($n=6$) among patients with early abdominal surgery. The mortality risk during the primary hospitalization after lung transplantation was significantly higher for patients who underwent an abdominal surgery in early course compared to those patients without such an operation, with a hazard ratio of 4.281 [confidence interval (CI) 1.773–10.532, $P=0.001$].

Late abdominal surgery after lung transplantation

Late abdominal problems requiring surgery occurred after a median of 37.9 months (IQR 15.6–80.1 months) after transplantation. The most common diagnosis was perforated diverticulitis, ileus, hernia, malignancy and symptomatic cholecystolithiasis, resulting in total of 89 interventions. The malignancies occurred in 8 different patients and included malignancy of the biliary system, colon carcinoma, carcinoma of small bowel and carcinoma of the liver. One of these patients died due to progression of malignancy. Overall, the most frequently affected organ was the small bowel

(23% of cases). In contrast to early abdominal events, the right colon was not affected, and mesenteric ischaemia was not observed as an indication for late surgery. Remarkably, 10 patients (19%) with late abdominal surgery were primarily hospitalized because of another disease, and the abdominal disease, bowel perforation and ileus developed secondarily. The primary reasons for hospitalization in those patients were pneumonia ($n=6$) or graft rejection and acute or chronic renal failure ($n=1$), encephalopathy ($n=1$), inguinal lymphocele ($n=1$) and leg ischaemia ($n=1$). In particular, diverticulitis ($n=10$, 19% of all late events) occurred in 4 cases after a primary hospitalization. Among 9 patients with ileus, only 1 patient had undergone a previous abdominal surgery.

A third (33%) of all late interventions showed an uneventful postoperative course, whereas major complications were observed in 30% of the elective and 55% of the emergency operations. A mortality of 19% was observed in patients with late abdominal surgery. There was no significant difference in mortality for elective or emergency late surgery ($P=0.09$). There is a significant correlation ($P=0.006$) between death after abdominal surgery and prior hospitalization because of a non-abdominal disease. In particular, 30% of patients with a complicated diverticulitis died within the hospitalization, reflecting less than 1% of the total cohort. Table 4 summarizes the degree of complications after late abdominal surgery.

Table 4: Severity of complications after late abdominal surgery

	Elective	Emergency	<i>P</i> -value
Clavien–Dindo (minor/major), <i>n</i> (%)	16 (70)/7 (30)	13 (45)/16 (55)	0.07
Grade 0	12 (52.2)	5 (17.2)	
Grade I	Not determined	Not determined	
Grade II	4 (17.4)	7 (24.1)	
Grade IIIa	0 (0.0)	1 (3.5)	
Grade IIIb	3 (13.0)	4 (13.8)	
Grade IVa	1 (4.3)	3 (10.3)	
Grade IVb	1 (4.3)	1 (3.5)	
Grade V	2 (8.7)	8 (27.6)	0.09

Long-term outcome after abdominal surgery in lung transplant patients

The median survival time of the whole population after lung transplantation ($n=315$) was 40.5 months (IQR 17–90 months) (Fig. 1). Thirty-day survival rate after lung transplantation was 94%. The overall survival rate at 1 and 5 years was 85% and 62%. Patients with early abdominal surgery had a median survival time of 31 months (IQR 2–74 months) compared to 40 months (IQR 16–85 months) in patients without any abdominal operation ($P=0.001$) and 90 months (IQR 35–114 months) in patients with late abdominal surgery ($P=0.002$). The median survival time of patients with late abdominal surgery was comparable with the survival time of patients without any abdominal surgery ($P=0.9$) (Fig. 2).

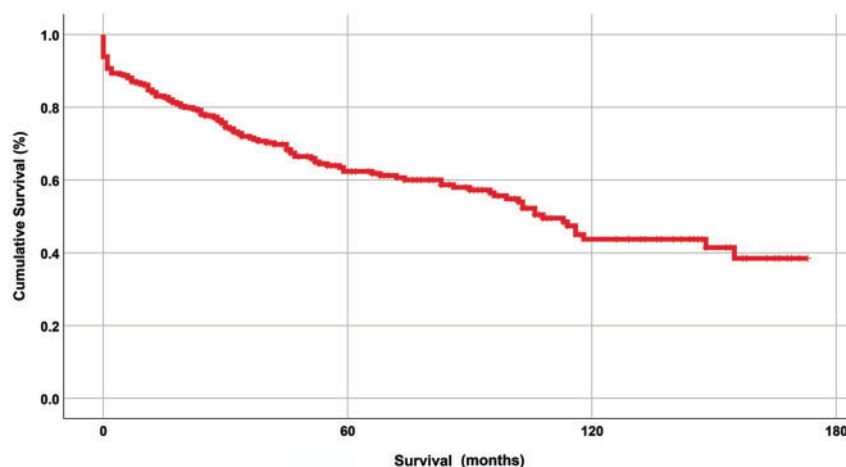


Figure 1: The Kaplan–Meier survival curve showing overall survival in all patients who underwent lung transplantation during the study period.

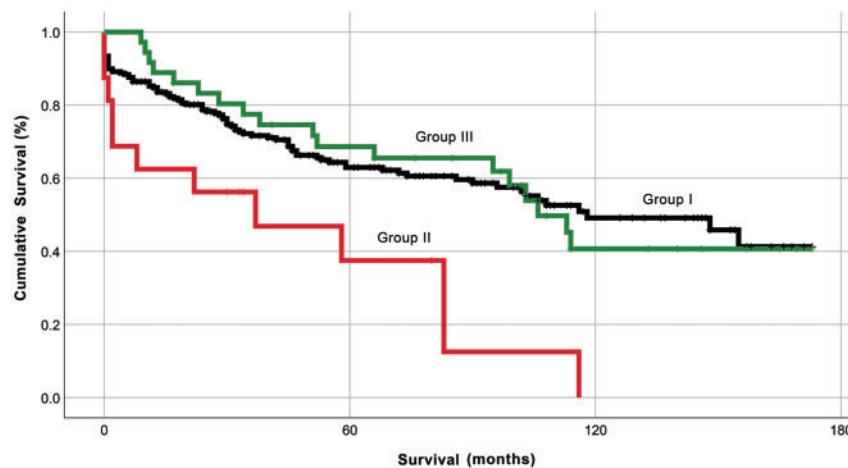


Figure 2: Survival of patients was divided into 3 groups. Group I (black line) represents patients without any abdominal surgery after lung transplantation ($n = 263$), Group II (red line) represents patients with early surgery ($n = 16$) and Group III (green line) represents patients with only late surgery, who never underwent abdominal surgery at early time points ($n = 36$).

DISCUSSION

In this cohort, 17% of lung transplant recipients were affected from abdominal disease requiring surgery. Overall, 5% of patients experienced early abdominal events and 13% experienced late abdominal events. This is in line with previous studies where the incidence of abdominal diseases requiring surgery varies between 7% and 21% depending on the definition of abdominal surgery and median time of follow-up [2–4, 8–10]. In the present study, the median follow-up was longer than other reports and may explain the higher incidence of abdominal surgery in our population [4, 8, 9]. Life-long severe immunosuppression requires additional medication to reduce the side effects of the immunosuppressive drugs. This polymedication appears to reduce the transit time of the intestinal content and also diminish signs and symptoms of abdominal disease. Abdominal complications, therefore, frequently occur in oligosymptomatic patients and require laboratory and imaging investigations for diagnosis as outlined in our published management guidelines [11].

A recent study in 2014 focussing on early abdominal surgery after lung transplantation described a laparotomy rate of 9%, with a median interval of 8 days after transplantation [9]. The most common cause for surgery was transmural unspecific inflammation in the right hemicolon. This corresponds well to our findings, with an interval of 7 days. Also, in the present series, bowel ischaemia of the right colon was the most common early indication and not observed as a late indication. There are only scarce data in the literature on why the right hemicolon is so vulnerable in the early post-transplant course after lung transplantation [12]. Severe hypotension as a result of surgery and the vulnerable blood supply of the right colon may be an explanation for the ischaemic events. The high mortality rate requires early recognition of symptoms, fast diagnosis and immediate treatment, despite unspecific clinical presentation and laboratory findings. CT angiography is only helpful in diagnosing mesenteric ischaemia at later stages, and the clinical judgement and experience are critically important [13].

In contrast, the most common late indication for abdominal surgery in this study was perforation of the descending colon and sigma due to diverticulitis. Complicated diverticulitis is a well-known problem in patients after lung transplantation, and prompt

detection and treatment are critical [14, 15]. It is still an open question whether or not to screen for diverticula and operate on patients for future lung transplantation to avoid later emergency interventions. However, there are important arguments against prophylactic surgery for diverticular disease. Diverticular disease is a frequent finding in the general population and associated with age [16], and recent guidelines from the American Gastroenterological Association do not recommend elective sigmoid resection after acute uncomplicated diverticulitis in the general population [17]. Although, perforated diverticulitis is the most frequent late abdominal disease requiring surgery in this cohort, it affects only 3% of lung transplant patients and is responsible for death in less than 1%. In addition, all patients with complicated diverticulitis in this series had no previous event of diverticulitis in their history. Consequently, prophylactic operations in patients without previous diverticular disease would probably produce more problems than they solve in lung transplantation candidates. Nevertheless, for selected patients with recurrent diverticulitis, a prophylactic operation before the transplantation can be considered [17]. In patients aged 50 years and older, we routinely perform a colonoscopy and gastroscopy to identify conditions that may predispose to intestinal complications such as diverticular disease, polyps, signs of inflammatory bowel disease or gastro-oesophageal reflux disease. Whether this strategy reduces intestinal complications requiring surgery cannot be assessed conclusively, but they are part of our routine evaluations resulting in the described overall complication rate.

The median survival time in the population from the Zurich University Hospital is favourable and consistent with the data from other studies [9, 18]. However, patients who underwent an abdominal surgery in the early course of transplantation have a significant higher postoperative mortality rate and a shorter median survival time. Therefore, special attention needs to be put on abdominal complaints in the first 7 days after transplantation.

In our study, COPD was a risk factor for developing late abdominal diseases requiring surgery after lung transplantation. Bredahl *et al.* [9] described alpha-1-antitrypsin deficiency as a risk factor for early abdominal surgery with an odds ratio of 5.74 (CI 2.15–15.35), although the frequency of alpha-1-antitrypsin deficiency was as high as 20% in the study population. Lahon *et al.* [19] described age and bilateral versus unilateral lung

transplantation as significant risk factors for developing early severe digestive complications. Grass *et al.* [8] found bilateral transplantation as a risk factor for gastrointestinal events as well. In addition, they identified a Charlson comorbidity index of ≥ 3 , matching with a higher age, as risk factor for developing gastrointestinal diseases. They concluded that older patients with several comorbidities and bilateral lung transplantation have an increased risk for developing abdominal complications. Contributing factors resulting from the transplantation itself would be interesting to identify, especially for early abdominal surgery, and, hence, need to be investigated in further studies. Our survival analysis comparing the outcome of early abdominal surgery and late abdominal surgery with those not requiring such surgery is likely limited by the selection bias. Because of the limited number of events and the fairly small population studied, we were not able to control for confounding factors in the respective populations. This should be addressed in larger studies.

CONCLUSION

In conclusion, gastrointestinal disease requiring surgery is common in lung transplant recipients. In particular, ischaemia of the right hemicolon in the early postoperative course and ileus and diverticulitis in the late postoperative course are important events. Early events are associated with a higher mortality rate and prolonged hospital stay, requiring immediate diagnosis and treatment. Abdominal operations at late time points have a favourable outcome unless patients were hospitalized prior to the abdominal complication.

Conflict of interest: none declared.

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